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TETRAHEDRAL INTERMEDIATES 4.[1] THE EFFECT OF CHLORO-SUBSTITUENTS ON THE KINETICS OF THE BREAKDOWN OF HEMIORTHOESTERS

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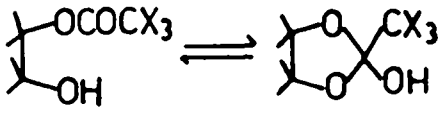
Abstract - 1-Hydroxy-2-chloromethyl-1,3-dioxolane (4) and 1-hydroxy-2-dichloromethyl-1, 3-dioxolane (5) have been detected as intermediates by ^{1}H NMR spectroscopy in the hydration of respectively 2-chloromethylene-1, 3-dioxolane and 2-dichloromethylene-1,3-dioxolane in aqueous acetonitrile. The kinetics of the breakdown of (4) and (5) into ethylene glycol monochloroacetate and monodichloroacetate have been studied by uv spectroscopy and values of k_{H^+}, k_{HO^-}, and k_{H_2O} evaluated. It was found that the introduction of chlorosubstituents into 2-hydroxy-2-methyl-1,3-dioxolane caused a decrease in k_{H^+} and increase in k_{HO^-} and little change in k_{H_2O} for its breakdown. The mechanisms of these reactions are discussed.

The stabilizing effect of three α-fluorosubstituents on hemiorthoesters, the tetrahedral intermediates of *O,O*-acyl transfer reactions, is well documented.[2-6] Thus, in acetonitrile solution pinacol monotrifluoroacetate, 1a, exists to the extent of 95% in the cyclic hemiorthoester form, (2a).[3] The stabilizing effect of three α-chlorosubstituents is rather less and pinacol trichloroacetate, (1b) exists only 13% in the cyclic hemiorthoester form, (2b). The values of ΔG° for formation of the hemiorthoesters from these esters therefore differ by about 2.9 kcal. mole^{-1}. This difference was thought to arise largely from steric hindrance to the formation of (2b).[3] When ethylene glycol monotrifluoro- and trichloroacetates were investigated no cyclic hemiorthoester could be detected by pmr.[3]



1 2
a X=F a X=F
b X=Cl b X=Cl

Guthrie and Cullimore have calculated by a semi-empirical method the equilibrium constants for the hydration of

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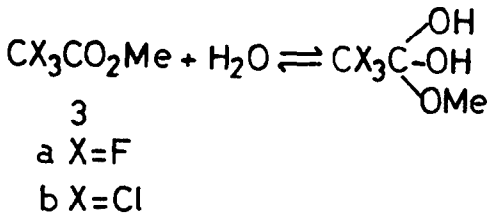
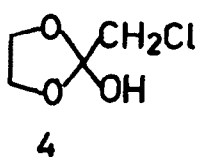


3
a X=F
b X=Cl

methyl trifluoroacetate, (3a) (log K°= -0.9) and methyl trichloroacetate, (3b) (log K° = -4.24).[5] Therefore according to these calculations formation of the hydrate is approximately 4.5 kcal. mole^{-1} more favourable from the trifluoroacetate than from the trichloroacetate. The calculated equilibrium constants for hydration of methyl dichloroacetate and methyl chloroacetate are more unfavourable with log K° = -4.34 and -6.66. Guthrie and Cullimore did not comment on the small difference between log K° for the hydration of the dichloro- and trichloro-acetates and it is possible that this may arise from a steric effect. Guthrie and Cullimore[5] also tabulated the rate constants for the hydronium-catalysed hydration of the esters. These vary very little on the introduction of the chloro- and fluoro-substitutents and so the major effect of these substituents on K° must be reflected in the rate constants for the hydronium-ion decomposition of the hydrates.

We have recently shown that cyclic hemiorthoesters may be generated in solution by the hydration of ketene acetals faster than they break down[6] and we now report the generation of cyclic hemiorthoesters (4) and (5) related to ethylene glycol monochloro- and dichloro-acetate and an investigation of the kinetics of their breakdown.



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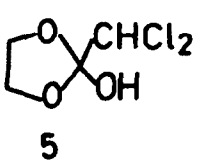

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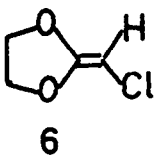

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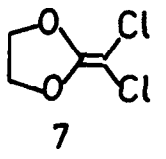

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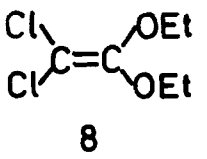

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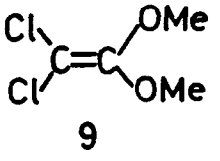

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EXPERIMENTAL

Materials. 2-Chloromethylene-1,3-dioxolane, (6), 2-dichloromethylene-1,3-dioxolane, (7), dichloroketene diethyl acetal, (8), dichloroketene dimethyl acetal, (9), were prepared by the method of McElvain and Curry[7] via the corresponding dichloroacetaldehyde or trichloroacetaldehyde acetal with potassium *tert*-butoxide in *tert*-butyl alcohol; (6) was stored at -80° to prevent polymerization, b.p. 88-90°C (20 mm) [lit.[7] 89-93°C (23 mm)]; NMR ($CDCl_3$) δ 4.33 (*s*, 4H), 4.65 (*s*, 1H). (7), b.p. 89-90°C (12 mm), m.p. 58-59°C [lit.[7] b.p. 118-121°C (12 mm), m.p. 55.5-57°C]; NMR ($CDCl_3$) δ 4.32 (*s*). (8), b.p. 77°C (20 mm) [lit.[8] 177°C (732-740 mm)]; NMR ($CDCl_3$) δ 3.8-4.1 (*q*, 4H), 1.21-1.37 (*t*, 6H). (9), b.p. 38°C (12 mm), NMR ($CDCl_3$) δ 3.70 (*s*).

NMR Measurements. These were carried out on a Perkin Elmer R32 spectrometer at 90 MHz. An NMR tube which contained a solution of the ketene acetal (0.15 M) in CD_3CN (0.4 ml) and tetramethylsilane was placed in the probe of the spectrometer at -40°. The lock signal was set and the spectrum run. The tube was removed from the probe, cooled to -80° and the required volume of D_2O/DCl or H_2O/HCl was added. After shaking it was placed in the probe, the lock signal was reset, and spectra were run at convenient temperatures and time intervals until conversion into the glycol monoester was complete.

Kinetic Measurements. These were carried out on a Pye Univam SP8-200 spectrophotometer operating online with a Commodore Pet 4016 microcomputer via an RS 232 interface. A stock solution of the ketene acetal in CH_3CN (ca. 0.3 M) (20 μL) was added to the prethermostatted reaction mixture (15.00 ±0.05°C), CH_3CN-H_2O (c_{H_2O} = 2.22 M or 8.33 M) which contained the required concentration of HCl, in a 10 mm quartz cuvette. 80 observations of the absorbance at 215 nm were taken by the computer at convenient time intervals via the RS 232 interface and the first-order

rate constant was calculated by a generalized least squares method.[9] The reaction was always followed to greater than 90% completion. The reactions in the alkaline limb of the pc_H-rate profile were studied by the "pH-jump" method (see ref.1). The ketene acetal was converted into the tetrahedral intermediate in an acidic solution and the required amount of sodium hydroxide solution (4×10^{-2} or 6×10^{-1} M) in H_2O-CH_3CN (c_{H_2O} = 2.22 M or 8.33 M) was added to bring the solution to the required pc_H which was measured at the end of each reaction. The pc_H's were determined as described previously[1] with a Radiometer PHM 64 pH-meter.

The variation of k with pc_H was fitted to eq. 1 using a generalized least squares method.[9] The values of K_w were taken from reference 1.

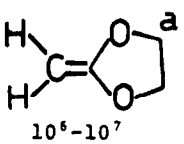
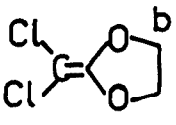
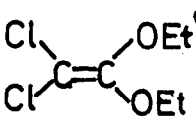
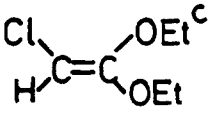
$$k = k_{H_2O} + k_{H^+}/10^{-pc_H} + k_{HO^-} \times K_w/10^{-pc_H} \quad (1)$$

RESULTS AND DISCUSSION

NMR experiments. We have recently shown that tetrahedral intermediates (hemiorthoesters) may be detected in the hydration of ketene acetals and the kinetics of their breakdown studied when they are generated in this way.[1,4,6] When chloro-substituents are introduced into ketene acetals they cause large decreases in the rate of hydration of ketene acetals (see Table 1).[10-12] Thus the introduction of two chloro-substituents into 2-methylene-1,3-dioxolane causes a 10^4-10^5 decrease in the rate of the H_3O^+-catalysed hydration and the introduction of a second chloro-substituent into chloroketene diethyl acetal causes a 10^3-10^4-fold decrease. Since decreases of these orders of magnitude might be expected in k_{H^+} for the breakdown of the resulting hemiorthoesters on the introduction of chloro-substituents (see above) it was thought that it might be possible to detect these species. This was found to be so with cyclic hemiorthoesters but was not possible with acyclic hemiorthoesters.

The ^1H NMR spectrum of 2-chloromethylene-1,3-dioxolane in CD_3CN at -40° consists of two signals at δ = 4.68 (*s*, 1H) and 4.34 (*s*, 4H) (Fig.1a). On addition of 5% D_2O-DCl so that the final concentration of DCl was 10^{-4} M the spectrum was transformed into that of 2-[$^2H_1$]-hydroxy-2-[$^2H_1$]-2-chloromethyl-1,3-dioxolane, δ = 3.94-4.12 (4H, *m*), 3.66 (1H, *bs*). This transformation was complete after 7 minutes at -30°. Then much more slowly signals of 2-[$^2H_1$]-hydroxyethyl 2-[$^2H_1$]-chloroacetate began to appear at δ = 4.22 (1H, *bs*), 4.17-4.23 (2H, *m*) and 3.61-3.72 (2H, *m*). After 45 minutes at -10°

Table I. The effect of chloro-substituents on the rate of hydration of ketene acetals at 25°

	 [a]	 [b]	 [c]	 [c]
$k_{H^+}/M^{-1}s^{-1}$	10^6-10^7	104	3.38	1×10^4

[a] Ref. 10.

[b] Ref. 11, the second-order constant given in Table I of this paper is in error by a factor of 100.

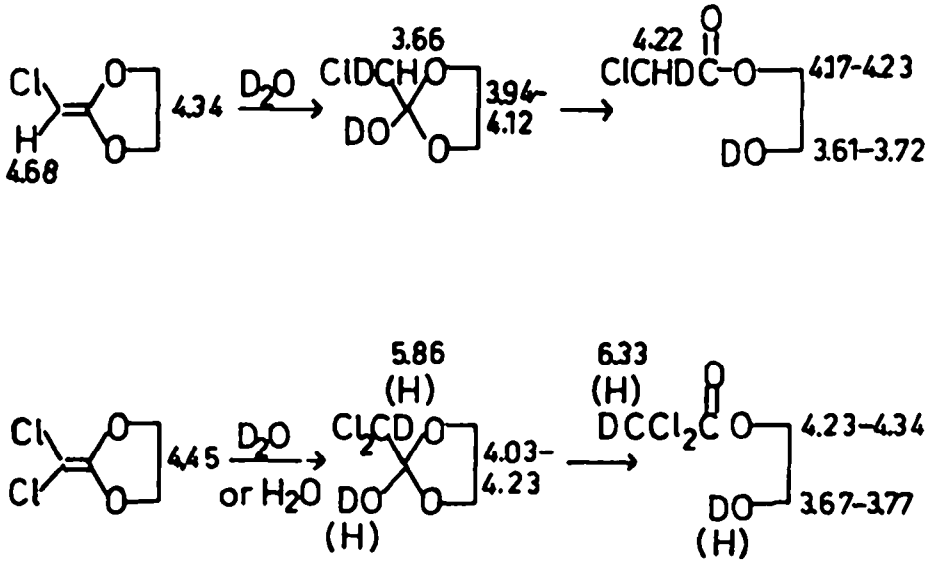
[c] Ref. 12.

this reaction was complete (fig. 1d). An experiment was also carried out using H_2O instead of D_2O and now signals corresponding to the chloromethyl group of the tetrahedral intermediate (δ = 3.66) and ester (δ = 4.22) were sharper and corresponded in intensity to two protons.

A similar series of experiments was carried out with 2-dichloromethylene-1,3-dioxolane (Fig. 2). When D_2O was used it was only possible to identify the tetrahedral intermediate by the signals of the ring protons (δ = 4.03-4.23) which were formed from the ring protons of the ketene acetal (δ = 4.45) and converted into the two multiplets of the product, ethylene glycol mono-[$^2H_1$]-dichloroacetate (δ = 4.23-4.34, 3.67-3.77). When H_2O was used however the signals of the dichloromethyl group of the intermediate at δ = 5.86 (s) and of product δ = 6.33 (s) were also detected. These results are summarised in Scheme 1.

Similar experiments were also carried out with dichloroketene diethyl and dimethyl acetals but no intermediate could be detected. This is readily explained since the cyclic ketene acetals undergo acid-catalysed hydration about 30 times more rapidly than the corresponding acyclic ones[12] whereas cyclic tetrahedral intermediates undergo acid-catalysed breakdown 50-60 times more slowly than the corresponding acyclic ones do.[3] Therefore the ratio of rate constants favourable for the detection of the cyclic tetrahedral intermediates becomes unfavourable with the acyclic tetrahedral intermediates. These NMR experiments therefore show that it should be possible to study the kinetics of breakdown of the cyclic tetrahedral intermediates 4 and 5 in the same way as the non-chlorine containing intermediates have been studied.[1,6]

Kinetic experiments. The kinetics of the disappearance of the chloro- and dichloro-ketene acetals and the formation of the corresponding esters were studied by following the change in absorbance at 215 nm. In CD_3CN-H_2O (c_{H_2O} = 2.22 M) only disappearance of the ketene acetal could be observed at pc_H's greater than *ca.* 7.6 and *ca.* 2.6 respectively for for the mono and dichloro-compounds. The values of k_{H^+} for these processes



Scheme 1

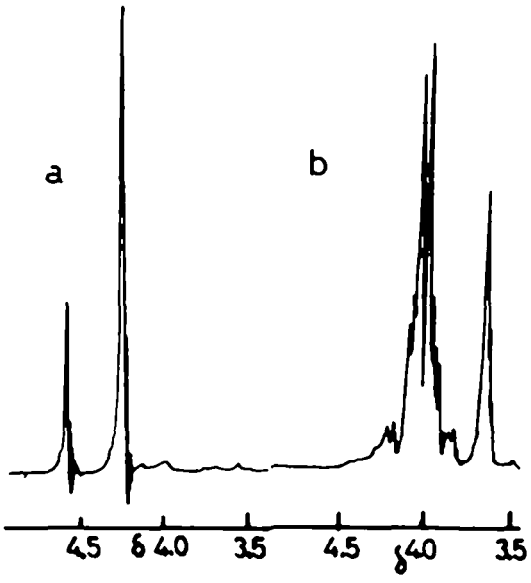


Fig.1. The hydration of 2-Chloromethylene-1,3-dioxolane

(a) 2-Chloromethylene-1,3-dioxolane (15 µl) in CD_3CN (0.400 ml) at -40°; δ = 4.68 (*s*, 1H), 4.34 (*s*, 4H).
(b) After addition of 5% D_2O-DCl. Final [DCl] = 10^{-4} M. 12 min. at -40° and 7 min. at -30°; conversion into 2-[$^2H_1$]-hydroxy-2-[$^2H_1$]-2-chloromethyl-1,3-dioxolane [δ = 3.94 - 4.12 (*m*) and 3.66 (*bs*)] is complete.
(c) After 27 min. at -30° and 13 min. at -20°; signals ascribed to 2-[$^2H_1$]-hydroxyethyl 2-[$^2H_1$]-chloroacetate are starting to appear: δ = 4.22 (*bs*), 4.17 - 4.23 (*m*), 3.61 - 3.72 (*m*).
(d) After a further *ca* 45 min. at -10°; conversion into 2-[$^2H_1$]-hydroxyethyl 2-[$^2H_1$]-chloroacetate is complete.

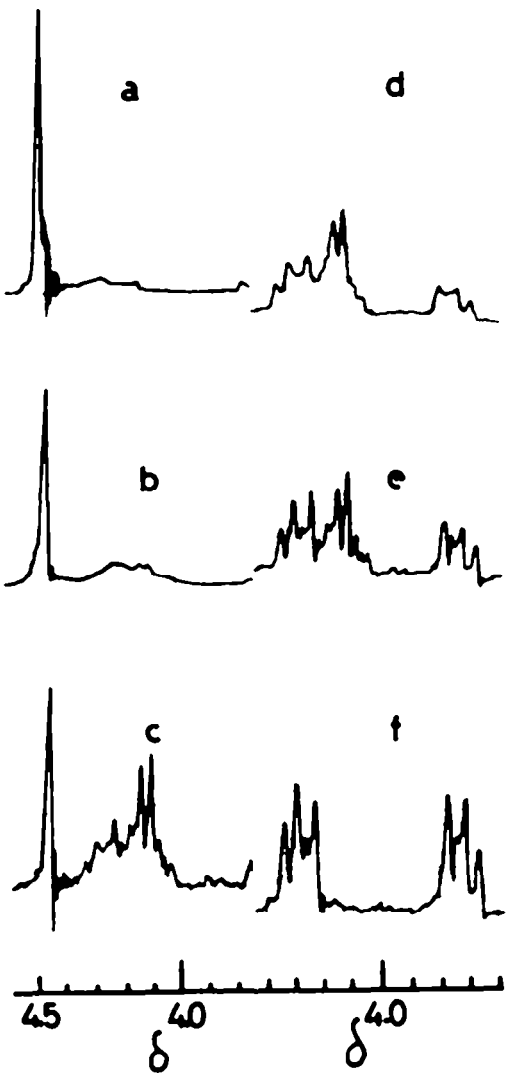


Fig. 2. The hydration of 2-Dichloromethylene-1,3-dioxolane

(a) 2-Dichloromethylene-1,3-dioxolane in CD_3CN at -40° (δ = 4.45).
(b) After addition of 4% D_2O-DCl at -40°; final concentration of DCl 2.66 x 10^{-4} M.
(c) After 8 min. at -40° and 27 min. at -20°. The signals of 2-deuteroxy-2-deutero-dichloromethyl-1,3-dioxolane at δ = 4.03 to 4.23 (*m*) are starting to appear. The signals of the product 2-hydroxyethyl deuterodichloroacetate at δ = 4.23 to 4.34 (*m*) and 3.67 to 3.77 (*m*) are also present.
(d) After a further 5 min. at -10°, 7 min. at 0°, and 18 min. at +10°.
(e) After a further 10 min. at +10°.
(f) Final spectrum after keeping 40 min. at +30°; just the signals of 2-hydroxyethyl deuterodichloroacetate are present.

and for the hydration of 2-methylene-1,3-dioxolane previously determined are given in Table II. It is seen that successive chlorine substitutions cause large rate decreases. Similar results were obtained with CH_3CN-H_2O (c_{H_2O} = 8.33 M) as solvent when the pc_H's above which only hydration of the ketene acetal was observed, were 3.3 and 2. At pc_H's lower than those mentioned above formation of the ester could be measured directly but at the higher pc_H the pH-jump method was used with the tetrahedral intermediate being generated in acid solutions and sufficient sodium hydroxide solution being added to adjust the pc_H to that required. The pc_H rate profiles are shown in Figs. 3 and 4 and the catalytic constants given in Tables III and IV.

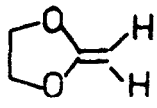
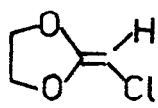
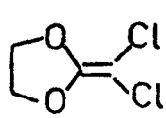
The most noticeable features of the results are that successive chloro-substitutions into 2-hydroxy-2-methyl-1,3-dioxolane cause a decrease in k_H+, and increase in k_{HO}- and little change in k_{H_2O} for the breakdown. The values of k_H+ are not correlated well by the σ^* constants, with the dichloro-compound reacting faster than expected, which suggests that steric effects may be important as previously proposed for the cyclization of pinacol mono-trichloroacetate.[3] Alternatively if OH bond breaking is occurring concertedly with O-C-bond breaking the substituent being varied would be acting perpendicular,[13] not parallel, to the reaction coordinate in which care a non-linear free energy relationship between log k_H+ and σ^* would be expected.

It is interesting to compare our results with the semi-empirical calculations of Guthrie and Cullimore[5] on the hydration of methyl esters. Guthrie and Cullimore calculated values of K°, the equilibrium constant for hydration, and from the rate constants k_w and k_H+ that they give for the formation of the hydrates it is possible to calculate rate constants k_w (d) and k_H+ (d) for the decomposition of the hydrates. These are given in Table V and the trend in k_H+ (d) on the introduction of chlorine substituents is qualitatively similar to that found by us.

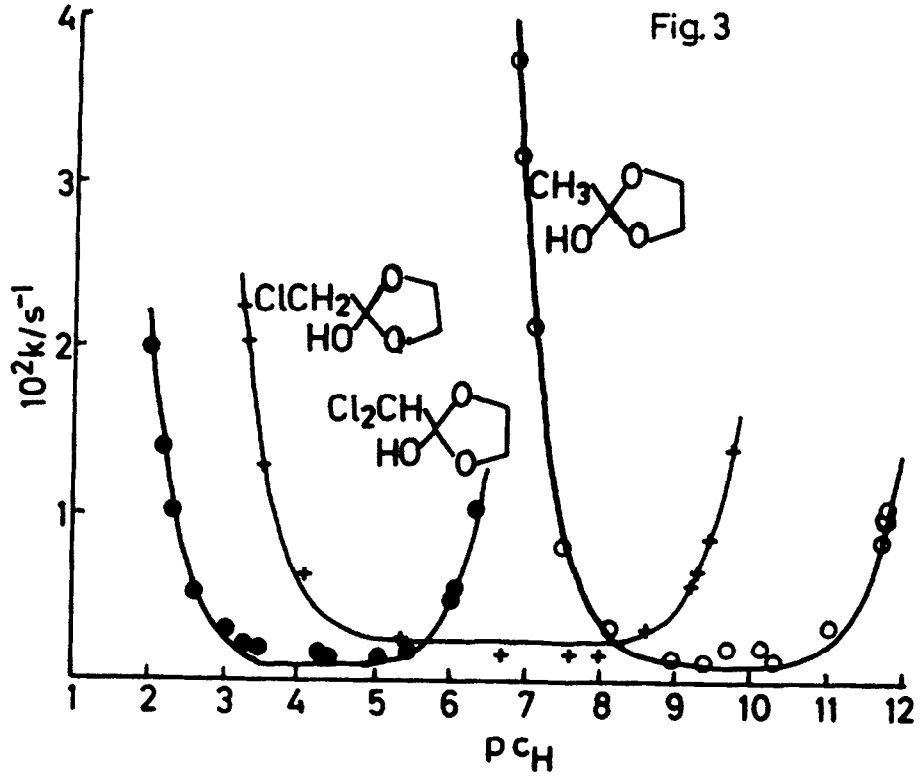
The effect on k_{H_2O} of introducing chloro-substituents into 2-hydroxy-2-methyl-1,3-dioxolane is small and this is also found on the constants based on Guthrie's and Cullimore's calculations for the breakdown of the ester hydrates.

As discussed in Part 3[1] the two most likely mechanisms are one in which ionization of the hydroxyl group is rate-limiting and a concerted process.[15] If ionization were rate-limiting the introduction of chloro-substituents

Table II. Rate constants for the hydronium-ion catalysed hydration of ketene acetals in acetonitrile-water mixtures at 15.00°C (units $M^{-1}s^{-1}$).[a]

c_{H_2O}/M			
2.22	9.36×10^{10}[b]	1.34×10^{7}	1.67×10^{2}
8.33		3.3×10^{2}	4.3

[a] Measured as the rate of disappearance of ketene acetal.
[b] Ref. 1.



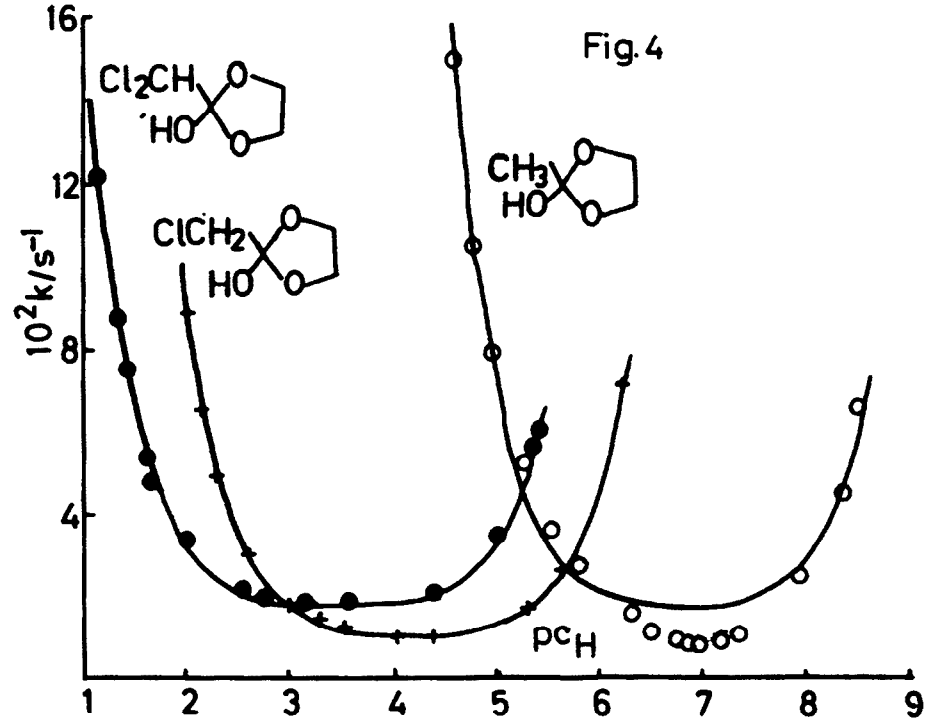


Fig. 3. Plot of $10^2k/s^{-1}$ against pc_H for the breakdown of 2-hydroxy-2-dichloromethyl-1,3-dioxolane (filled circles); 2-hydroxy-2-chloromethyl-1,3-dioxolane (crosses) and 2-hydroxy-2-methyl-1,3-dioxolane (open circles) (ref. 1) at 15° in CH_3CN-H_2O (c_{H_2O} = 2.22 M).

Fig. 4. Plot of $10^2k/s^{-1}$ against pc_H for the breakdown of 2-hydroxy-2-dichloromethyl-1,3-dioxolane (filled circles), 2-hydroxy-2-chloromethy-1,3-dioxolane (crosses) and 2-hydroxy-2-methyl-1,3-dioxolane (open circles) (ref. 1) at 15° in CH_3CN-H_2O (c_{H_2O} = 8.33 M).

Table III. Catalytic constants for the breakdown of hemiorthoesters in $CH_3CN:H_2O$ (c_{H_2O} = 8.33 M) at 15.00 ±0.05°C.[a]

$k_H+/M^{-1}s^{-1}$	$10^{10}k_{HO}-/M^{-1}s^{-1}$	$10^2k_{H_2O}$
2-Hydroxy-2-dichloromethyl-1,3-dioxolane		
1.47(0.0087)	2460(36)	1.60(0.038)
2-Hydroxy-2-chloromethyl-1,3-dioxolane		
7.91(0.035)	536(3.4)	0.89(0.022)
2-Hydroxy-2-methyl-1,3-dioxolane[b]		
5500(153)	1.97(0.19)	1.53(0.24)

[a]Calculated by fitting the experimental results to equation 1 using a generalized least squares method. The figures in brackets are standard deviations.

[b]Results from ref. 1.

Table IV. Catalytic constants for the breakdown of hemiorthoesters in $CH_3CN:H_2O$ (c_{H_2O} = 2.22 M) at 15.00 ±0.05°C.[a]

$k_H+/M^{-1}s^{-1}$	$10^{10}k_{HO}-/M^{-1}s^{-1}$	$10^4k_{H_2O}/s^{-1}$[b]
2-Hydroxy-2-dichloromethyl-1,3-dioxolane		
1.87(0.025)	2640(72)	4.9(1.5)
2-Hydroxy-2-chloromethyl-1,3-dioxolane		
36.3(0.86)	1.32(0.067)	23(3.5)
2-Hydroxy-2-methyl-1,3-dioxolane[c]		
2.58×10^5 (2.92×10^3)	0.00899(0.00043)	7.9(3.2)

[a]Calculated by fitting the experimental results to equation 1 using a generalized least squares method. The figures in brackets are standard deviations.

[b]The standard deviations on k_{H_2O} are so high that these constants are not well defined.

[c]Results from ref. 1.

Table V. Rate constants for the breakdown of ester hydrates in water at 25° based on calculations by Guthrie and Cullimore[5]

	$k_w(d)/s^{-1}$	$k_H+(d)/M^{-1}s^{-1}$
$CH_3C(OH)_2OMe$	.135	1.78×10^4
$ClCH_2C(OH)_2OMe$	1.66	3.47×10^2
$Cl_2CHC(OH)_2OMe$	0.48	4.68, 0.27

should cause a rate increase as the hydroxyl group should become more acidic and the recombination of the anion with H_3O^+ should remain at the diffusion controlled limit. The observation that no increase is observed therefore suggests that this mechanism is not correct and that a concerted mechanism[15] is a better formulation.

The rate increasing effect of chloro-substituents on k_{HO^-} could be explained on the basis of the proposed mechanism[1] as arising from a more favourable equilibrium for the formation of the anion. However, with these more reactive species derived from chloroacetic or dichloroacetic acid the experimental results may be explained better by a mechanism in which there is a rate-limiting ionization or one in which there is concerted breaking of O-H and C-O bonds.

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